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Vitamin Supplementation for Cardiovascular Protection: Salutary, Superfluous or Sinister? A Brief Review

Shashi K Agarwal

Medical Director, Agarwal Health Center, NJ, USA

Correspondence to: Shashi K. Agarwal, MD, FACP, FACC, FAAIM; Email: usacardiologist@gmail.com; Ph:- 732-895-3200

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ABSTRACT

Vitamins are commonly prescribed for a host of medical conditions. Vitamins are also extensively consumed as a dietary supplement by otherwise healthy people. This use emanates from a widespread belief that they are beneficial for health. Cardiovascular disease is the number one killer in the world. The use of vitamin supplements to prevent cardiovascular diseases is very common. However, large well controlled clinical trials have failed to conclusively prove this benefit for most vitamins. This brief review looks at evidence based data on the cardiovascular protective effects of vitamin supplements.

Key words: anti-oxidants, cardiovascular disease, beta-carotene, vitamin A, vitamin B, vitamin C, vitamin D, vitamin E

Abbreviations: CV: Cardiovascular; CVD: Cardiovascular disease; WHO: World Health Organization

1. INTRODUCTION

Cardiovascular disease (CVD) is the world's leading killer (WHO, 2013). Oxidative damage and production of free radicals in the endothelium, with oxidative modification of the low density lipoprotein (LDL) is a major factor in the development and progression of the atherosclerotic pathology resulting in CVD (Bruckdorfer, 2008). Antioxidants trap organic free radicals and de-active excited oxygen molecules. Besides decreasing atherosclerotic plaque, antioxidants can also preserve endothelial function, inhibit platelet agreeability and decrease thrombotic potential (Salonen, 1989). A higher dietary intake of antioxidant nutrients is associated with a lower risk of CVD (Stampler et al., 1993; Rimm et al., 1993). Vitamins A, C and E have significant anti-oxidant properties. Clinical studies have demonstrated

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that high ascorbate levels (Khaw et al., 2001) and high dietary vitamin E intakes (Kushi et al., 1996) were associated with a reduced risk of CVD. B vitamins, especially folic acid, B6 and vitamin B12, lower homocysteine, high levels of which have been associated with cardiovascular disease (Boushey et al., 1995). Vitamin D has several effects on the heart, vasculature and the renin-angiotensin function (Bouillon et al., 2008), and has shown to have an inverse relationship between its levels and cardiovascular disease and mortality (Grandi et al., 2010; Pittas et al., 2010). Given data from a large collection of epidemiological, experimental, clinical and intervention studies, it appears that most vitamin deficiencies are closely related to the development and progression of cardiovascular disease (Stampfer et al, 1993; Rimm et al., 1993; Khaw et al., 2001; Kushi et al., 1996; Yochum et al., 2000). However, whether vitamin deficiencies reflect unhealthy cardiovascular life styles or impart a direct causal effect, has been unclear (Kris-Etherton et al., 2004). Scientific data has been disappointing when it comes to supplementation with these vitamins and the anticipated decrease in cardiovascular events and mortality (Asplund et al., 2002). This brief review was done primarily by querying PubMed entries relating to these vitamins and cardiovascular disease. Other relevant resources were also used to further investigate any association. Supplementation with vitamin K is rare and this vitamin was not included in the review.

2. DISCUSSION

2.1. Vitamin A

Beta-carotene has significant anti-oxidant properties and is often used as a supplement to prevent cardiovascular disease. PubMed showed 770 entries dating back to 1960 under vitamin A and cardiovascular disease.

2.1.1. Data Review

Several observational studies, including ecological, cohort and case-control studies support a role of beta-carotene in the prevention of cardiovascular disease especially coronary heart disease (Gey et al., 1993; Street et al., 1994). There was a stronger protection noted in smokers. However, three of the four major published randomized clinical trials of beta-carotene supplementation found increases in cardiovascular disease mortality in the supplemented groups ranging from 12 to 26% (The Alpha-Tocopherol Beta Carotene Prevention Study Group, 1994; Greenberg et al., 1999; Omenn et al. 1996). No difference was noted in The Physicians Health Study (Hennekens et al. 1996). Smokers appeared to have more adverse effects from supplementation. In the Beta Carotene and Retinol Efficacy Trial (CARET), the relative risk of death by lung cancer increased by 17% in the β-carotene supplemented heavy smokers vs. placebo group. Published data therefore indicates a major discrepancy between observational and interventional studies. Overall, supplementation with beta carotene was associated with an increase in all-cause as well as cardiovascular mortality. Negative interactions have also been noted between beta-carotene and some anti-lipid drugs including statins, niacin, cholystytramine and orlistat.

2.1.2. Clinical Implications

Despite the suggestion from observational studies, several large randomized controlled trials not only have failed to confirm the benefits for beta-carotene supplementation in cardiovascular disease prevention, but suggest a deleterious effect, with smokers and those exposed to asbestos being more prone. Non-dietary pharmaceutical supplementation with beta-carotene is therefore sinister. Anti-oxidant cardiovascular protection is best achieved by consuming fruits and vegetables rich in this precursor to vitamin A.

2.2. Vitamin B

A large number of epidemiological studies have established that an elevated level of total homocysteine in blood is associated with atherosclerotic vascular disease in the coronary, cerebral, and peripheral vessels, and for arterial and venous thromboembolism (Boushey et al., 1995). Hyperhomocysteinemia results from commonly occurring genetic and acquired factors, which include deficiencies of folate and vitamin B12. Supplementation with these vitamins has been therefore suggested as an easy and effective way to reduce homocysteine levels and provide cardiovascular protection. A total of 8821 entries dating back to 1946 were found under vitamin B and cardiovascular diseases on PubMed.

2.2.1. Data Review

Observational studies have reported inverse associations of cardiovascular disease with dietary intake or plasma concentrations of B vitamins (Morrison et al., 1996; Rimm et al. 1993 & 1998). Dietary supplementation with folic acid and B vitamins has shown to reduce plasma total homocysteine concentration (HLTC), raising the prospect of a reduction in coronary heart disease and stroke. Several large scale trials (HOPE-2, VITATOPS, VISP, WAFACS) have examined the effects of supplementation with B vitamins on cardiovascular disease (VITATOPS, 2010; Lonn et al.

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2006), but none has reported any significant effects on the risk of developing cardiovascular disease or any reduction in major cardiovascular events.

2.2.2. Clinical Implications

Moderately elevated concentrations of plasma total homocysteine have been associated with higher risks of cardiovascular disease, especially coronary heart disease and stroke. Although a causal relationship has not been established, it had been suggested that supplementation with B vitamins to reduce homocysteine levels should slow the progression of atherosclerosis and this should translate into a reduction of cardiovascular events (Toole et al. 2004). This has not been proven in several well controlled trials. Supplementation with B vitamins for cardiovascular protection is not supported by scientific data and is therefore superfluous (Homocysteine Lowering Trialists' Collaboration, 2005).

2.3. Vitamin C

Ascorbic acid is a strong anti-oxidant and is potentially involved in cardiovascular protection. Besides it anti-oxidant effects, vitamin C is also known to beneficially modulate lipid levels and exert a hypotensive effect. We found 3750 entries dating back to 1945 when searched under vitamin C and cardiovascular diseases on PubMed.

2.3.1. Data Review

Scientific studies have shown inconsistent association between supplemental vitamin C and cardiovascular disease. Epidemiological studies and clinical trials have shown significant reduction in CVD (Enstrom et al., 1992; Knekt et al., 2004), while other studies have revealed an inverse association (Ascherio et al. 1999). Several studies have shown no effect (Messerer et al., 2008; Buijsse et al., 2008). In a recent, large scale and well controlled trial, vitamin C supplementation did not reduce the risk of major cardiovascular events (The Physicians' Health Study II). There was no difference between patients receiving vitamin C or placebo in the incidence of MI, embolic or hemorrhagic stroke or all-cause mortality after 8 years of treatment and follow up in 14,641 men. It is therefore prudent to conclude that the role of vitamin C supplementation in the prevention of CVD is non-existent or inconclusive.

2.3.2. Clinical Implications

Despite the suggestion from observational studies, a large randomized controlled trial failed to confirm the benefits for vitamin C supplementation in cardiovascular disease prevention. Although some reports suggest a positive and some a negative effect, the overall association is neutral. Non-dietary pharmaceutical supplementation with vitamin C is therefore superfluous in the context of cardiovascular protection. Vitamin C related cardiovascular protection is best achieved by consuming fruits and vegetables rich in this vitamin.

2.4. Vitamin D

Recent epidemiological, experimental and clinical evidence has suggested that low vitamin D levels may play a role in various cardiovascular conditions, including hypertension, coronary artery disease, congestive heart failure, valvular calcification, vascular dysfunction and stroke. An estimated 1 billion people in the world have vitamin D deficiency or insufficiency, and undiagnosed vitamin D deficiency is common. Vitamin D metabolites have significant actions on cardiomyocytes, and endothelial and vascular smooth muscle cells. Vitamin D is obtained from sunlight and to a smaller degree from food. Supplementation is easy, safe and effective. All entries under vitamin D and heart/cardiovascular disease listed on PubMed were reviewed. We found 3337 entries dating back to 1947.

2.4.1. Data Review

Robust epidemiological and clinical evidence has linked vitamin D deficiency with hypertension, myocardial infarction, and stroke (Al Mheid et al., 2013; Motivala et al. 2012). It has also been associated with diabetes, left ventricular hypertrophy, congestive heart failure, peripheral vascular disease, atherosclerosis, and endothelial dysfunction. Vitamin D deficiency may cause vascular smooth muscle cell proliferation, endothelial cell dysfunction, vascular and myocardial cell calcification, rennin-angiotensin system activation and increased inflammation. Although a direct causal relationship remains to be established, the association has been proved in many clinical studies (Tompson et al. 2013). Vitamin D levels were associated with an increased all-cause and cardiovascular mortality in patients undergoing coronary angiography (Dobnig et al. 2008). Emerging data is supporting vitamin D supplementation. A meta-analysis of 18 independent randomized controlled trials of more than 57000 participants, revealed a relative risk reduction for all-cause mortality by 7% with therapeutic vitamin D replacement (Autier et al. 2007). Another meta-analysis of 8 randomized trials revealed a slight 10% reduction in CV disease risk with approximately 1000 mg/day vitamin D supplementation (Wang et al. 2010). A more recent study revealed that a 20% lower vascular

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mortality and 23% lower non-vascular mortality resulted by supplementation aimed at achieving a two-fold higher plasma concentration of 25(OH)D (Tomson et al., 2013). Vitamin D appears to be a genuine cardio-protective agent.

2.4.2. Clinical Implications

Vitamin D deficiency is extremely prevalent. Deficiency results from decreased exposure to sunlight, and to a lesser degree from low dietary intake of vitamin. Other factors may be involved. Deficiency may be a biomarker of an unhealthy cardiovascular lifestyle. The association between vitamin D deficiency and substantial increases in the incidence of hypertension, hyperlipidemia, myocardial infarction and stroke, as well as chronic kidney disease and type 2 diabetes has been well established. It is also associated with increased cardiovascular events and an increased all cause and cardiovascular mortality. Supplementation with vitamin D appears to favorably impact several disease conditions and reduces all cause and cardiovascular mortality. Although most people will require pharmaceutical supplementation, its deficiency can also be prevented and corrected by adequate exposure to sunlight and eating vitamin D rich foods such as salmon and mackerel. Vitamin D supplementation for cardiovascular protection in those deficient, appears to be salutary.

2.5. Vitamin E

Alpha-tocopherol (vitamin E) is a fat-soluble antioxidant vitamin. In mouse models, it has shown to prevent atherosclerotic plaque formation. This vitamin has therefore been touted as a potential nutrient for cardiovascular protection. A review of PubMed revealed 4173 entries dating back to 1947 under vitamin E and cardiovascular disease.

2.5.1. Data Review

Several observational and epidemiological studies have shown higher vitamin E dietary intake with lower risk of CV events (Jha et al., 1995). However the Hope study found that treatment with vitamin E for a mean of 4.5 years had no apparent effect on cardiovascular outcomes (Yusuf et al. 2000). A subsequent meta-analysis of randomized controlled studies concluded that high dose vitamin E supplementation may increase all-cause mortality (Miller et al. 2005). In the more recent Physicians' Health Study II (Sesso et al. 2008), there was no difference between patients receiving vitamin E or placebo in the incidence of major cardiovascular events, including myocardial infarction, stroke, congestive heart failure, or all-cause mortality. However, there was a significant increase in the risk of hemorrhagic stroke in the vitamin E arm when compared to the placebo arm.

2.5.2. Clinical Implications

Despite the suggestion from observational studies, meta-analysis of several controlled studies and a large randomized controlled trial not only failed to confirm the benefits for vitamin E supplementation in cardiovascular disease prevention, but demonstrated an increase in the risk of hemorrhagic stroke and all cause mortality. Non-dietary pharmaceutical supplementation with vitamin E may therefore be sinister when used for cardiovascular event protection. Cardiovascular preventive measures based on antioxidant supplementation with vitamin E are therefore not justifiable. A diet rich in foods abundant in the antioxidant vitamin E is the preferred choice for this purpose.

3. CONCLUSION

Vitamins are commonly consumed as a non-prescription pharmaceutical supplement. There is a strong perception that they protect against cardiovascular disease. However, large scale, well controlled, randomized clinical trials have failed to substantiate this benefit for most vitamins (Vivekananthan et al., 2003). Antioxidants may not play a significant role in modern management of atherosclerosis (Steinberg et al., 2002), and may even act as pro-oxidants (Stocker, 1999). As a matter of fact, supplementation is often associated with deleterious outcomes. Only vitamin D appears to have a salutary effect on cardiovascular disease and mortality, when supplemented in deficient individuals. However, further data on this vitamin is still emerging. The cardiovascular connection with vitamin C is largely neutral, and may be marginally positive or negative. In general, intake of vitamin C for cardiovascular disease prevention appears to be superfluous. B vitamin supplementation is also superfluous when considered in the context of cardiovascular protection. B carotene supplementation is harmful, especially in smokers and those exposed to asbestos. Vitamin E is also sinister, as it appears to cause an increase in hemorrhagic stroke. A diet rich in fruit and vegetables (La Vecchia, 1998; Hu, 2003) and a healthy lifestyle with sufficient exposure to sunlight (Wallis et al., 2008) is more beneficial for cardiovascular health than any cocktail of pharmaceutical vitamins.

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